



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> A01N 59/16, 25/34, 25/12 A61L 29/00, 2/00, A61K 33/38	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 90/08470</b>  <b>(43) International Publication Date:</b> 9 August 1990 (09.08.90)
<b>(21) International Application Number:</b> PCT/GB90/00125 <b>(22) International Filing Date:</b> 29 January 1990 (29.01.90)  <b>(30) Priority data:</b> 8901846.9      27 January 1989 (27.01.89)      GB 8902785.8      8 February 1989 (08.02.89)      GB 8904806.0      2 March 1989 (02.03.89)      GB  <b>(71) Applicant (for all designated States except US):</b> GILTECH LIMITED [GB/GB]; 11/12 North Harbour Estate, Ayr KA8 8AA (GB).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only) :</b> GILCHRIST, Thomas [GB/GB]; 67 Midton Road, Ayr KA7 2TW (GB).  <b>(74) Agent:</b> PATTULLO, Norman; Murgitroyd and Company, Mitchell House, 333 Bath Street, Glasgow G2 4ER (GB).		<b>(81) Designated States:</b> AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.  <b>Published</b> <i>With international search report.          Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> A MEDICINAL SUBSTANCE FOR TOPICAL APPLICATION  <b>(57) Abstract</b>  A medicinal substance for topical application is disclosed. The substance comprises a water-soluble glass containing silver or a silver compound. Typically, the glass comprises phosphorus pentoxide and contains silver oxide. The substance may be used for the treatment of wounds, catheter and tubing entry points, stoma sites and body passage entrances where bacterial growth and migration are rife. The glass may be in the form of a powder, granules, woven into a dressing form, a sinter shaped in a particular way or used as filler in polymers for surface release.		

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1   A Medicinal Substance for Topical Application

2

3

4   This invention relates to an antimicrobial composition  
5   for use in medicine. The invention also relates to a  
6   device for use in medicine, which embodies the said  
7   composition and to a method of inhibiting or combating  
8   infection.

9

10   This invention also relates to an antimicrobial  
11   composition for use in topical applications.

12

13   The antimicrobial action of silver ions is well known  
14   as are pharmaceutical formulations containing silver  
15   salts as active principle. Perhaps the best known  
16   example of such materials is silver sulphadiazine.  
17   However, silver nitrate and silver allantoinate are  
18   also used as antimicrobials.

19

20   In addition, many wounds, especially burns, are subject  
21   to contamination by organisms such as bacteria and  
22   fungi. The use of silver as an antiseptic agent in  
23   medicine is well-known, and a variety of topical  
24   preparations based on silver salts are used in the  
25   treatment of such infected wounds eg silver nitrate and

1 silver allantoate. However, problems associated with  
2 such compounds include pain on application, staining  
3 and skin irritations. Improved substances such as  
4 silver sulfadiazine are commonly used, but they must be  
5 removed and re-applied frequently to maintain their  
6 effect. These compounds themselves can adverse cause  
7 reactions in some patients, for example a reduction in  
8 the number of leucocytes in the local area available  
9 for fighting infection in the wound and this method of  
10 treatment also results in regular disturbance of the  
11 wound, which causes discomfort to the patient.

12  
13 The use of glasses which can dissolve in water and body  
14 fluid and which are applied internally of the body are  
15 well-known. These glasses are formed from phosphorus  
16 pentoxide and may be modified to dissolve over a period  
17 of minutes, months or even years, as required. To  
18 date, such glasses have been used, in medicine, for the  
19 controlled release of a number of agents, for example,  
20 drugs, hormones and trace elements, but in each case  
21 the glass has been applied internally of the body to  
22 allow the agent to leach out into the body's  
23 circulatory system.

24  
25 It is known that certain glasses, in which the usual  
26 glass former, silicon dioxide, of traditional glasses  
27 is replaced with phosphorus pentoxide as the glass  
28 former, are soluble in water and body fluids. The rate  
29 of dissolution is controlled largely by the addition of  
30 glass modifiers such as calcium and magnesium oxide.  
31 In simple terms, the greater the concentration of the  
32 modifier the slower is the rate of dissolution. The  
33 rates of dissolution which can be imparted to the  
34 glasses may range from minutes to months or even to  
35 several years. It is known to include in such

1 compositions quantities of trace elements such as  
2 copper, cobalt and selenium which will be released from  
3 the glass as it slowly dissolves over the selected  
4 period of time.

5  
6 The use of water-soluble glasses has been described for  
7 a variety of purposes in the literature. For example,  
8 UK Patent Specifications numbers 1,565,906, 2,079,152,  
9 2,077,585 and 2,146,531 describe the gradual  
10 dissolution of the glasses as providing a means of  
11 controlled release of drugs, hormones, fungicides,  
12 insecticides, spermicides and other agents with which  
13 the glasses have been impregnated. The glasses are  
14 used for example in the form of an implant or bolus.

15  
16 UK Patent Specification number 2,030,559 describes the  
17 use of selenium-impregnated water-soluble glass for  
18 providing controlled release of the selenium as a trace  
19 element into cattle and sheep, the glass being applied  
20 as a subcutaneous insert. UK Patent Specification  
21 number 2,037,735 also describes a subcutaneous implant  
22 of water-soluble glass, and in this case the glass is  
23 impregnated with copper; minor quantities of trace  
24 elements such as boron, arsenic, iodine, manganese,  
25 chromium, silver, gold and gallium may also be  
26 included.

27  
28 Water-soluble glass has also been proposed for use in  
29 prosthetics, for example in UK Patent Specification  
30 number 2,099,702, and for use in anticorrosive paints,  
31 as described in UK Patent Specification number  
32 2,062,612. Further the literature provides for the use  
33 of such glasses in the controlled release of ferrous  
34 and ferric ions into the human or animal body by  
35 ingestion or implantation of the glass (UK Patent

1 Specification number 2,081,703), and for the use of  
2 glasses in the controlled release of ions such as  
3 lithium, sodium, potassium, caesium, rubidium,  
4 polyphosphate, calcium and aluminium to patients by  
5 inclusion of the glass in a drip feed line (UK Patent  
6 Specification number 2,057,420).

7  
8 Our International Patent Application No PCT/GB 88/00701  
9 relates to apparatus for antimicrobial use in passage  
10 of fluid to or from a living body, the apparatus  
11 comprising a conduit for insertion into the body, a  
12 reservoir for fluid and a connector member for  
13 connecting said conduit to said reservoir external of  
14 the body, wherein said connector member includes a  
15 water-soluble glass impregnated with elemental silver  
16 or a compound of silver, said water-soluble glass  
17 defining at least a part of a passageway for fluid to  
18 flow between the reservoir and the conduit.

19  
20 The apparatus preferably contains the impregnated  
21 water-soluble glass at a site at which bacteria can be  
22 introduced or increased in number, and the  
23 bacteriostatic or bactericidal properties of the silver  
24 has the effect of containing or reducing the risk of  
25 infection in the body. The connector member may  
26 comprise a first portion having an end adapted for  
27 connection with said conduit and a second portion  
28 having an end adapted for connection with said  
29 reservoir, the first and second portions being  
30 releasably secured together to define a fluid  
31 passageway between the reservoir and the conduit and at  
32 least one of the first and second portions having an  
33 internal lining of said impregnated water-soluble  
34 glass. The internal lining may be retained between  
35 spaced shoulders on the first or second portion, so

1 that when the portions are separated the lining is held  
2 in position until re-connection is made.

3  
4 The connector member may be in the form of a fitting  
5 which connects together upstream and downstream tubing,  
6 each of the first and second portions of the connector  
7 being disposed at an end of the respective tubing. If  
8 it becomes necessary to disconnect the tubing remote  
9 from the patient, for example to replace a full  
10 reservoir of fluid drained from the patient with a full  
11 one, the connector can be broken and the silver reduces  
12 the danger of infection to the patient through ingress  
13 of bacteria.

14  
15 The connector member may consist of or include a length  
16 of tubing, for example of plastics material, rubber or  
17 silicone rubber, in which the impregnated water-soluble  
18 glass is dispersed so that the silver is released from  
19 the tubing wall.

20  
21 The reservoir may also contain impregnated  
22 water-soluble glass, especially in the case where fluid  
23 is being drained from the patient, for example in urine  
24 drainage systems. During collection of the urine in  
25 the reservoir in conventional systems bacteria multiply  
26 and there is a risk that they may migrate along the  
27 drainage tubing to the patient, thereby increasing the  
28 incidence of bacteria and producing urinary tract  
29 infection. Inclusion in the reservoir of an apertured  
30 container in which silver-impregnated water-soluble  
31 glass is disposed prevents the multiplication of  
32 bacteria in the reservoir and therefore reduces the  
33 infection risk. A preferable form of container has  
34 been found to be a flexible braided polyester sleeve  
35 closed at each end to form an elongate pouch and

1 containing granules of the glass. This system also  
2 protects nursing staff, who are required to replace  
3 full reservoirs, and/or to drain off urine from full  
4 reservoirs, by preventing proliferation of bacteria in  
5 the urine.

6  
7 The apparatus may be used for example in urine drainage  
8 systems, post-surgical drainage systems, cannula  
9 systems and renal and peritoneal dialysis systems.

10  
11 There is also provided a connector member having an  
12 inlet and an outlet and having walling defining a  
13 through passageway for flow of liquid from the inlet to  
14 the outlet, at least a part of said walling being  
15 formed of water-soluble glass impregnated with  
16 elemental silver or a compound of silver.

17  
18 According to one aspect of the present invention, there  
19 is provided a medicinal substance for topical  
20 application which comprises a water-soluble glass  
21 containing elemental silver or a silver compound, and  
22 means to maintain the substance in contact with a  
23 surface of a body.

24  
25 According to a second aspect of the invention there is  
26 provided a method of retarding bacterial growth at the  
27 surface of a body, comprising applying to the surface  
28 water-soluble glass impregnated with elemental silver  
29 or a silver compound, and maintaining the glass in  
30 contact with the surface.

31  
32 According to a third aspect of the invention there is  
33 provided the use of water-soluble glass containing  
34 elemental silver or a compound of silver in the  
35 preparation of a medicament for the treatment of wounds



1 and other topical infection sites.

2

3 The invention can be employed, for example, in treating  
4 wounds, catheter and tubing entry points, stoma sites  
5 and body passage entrances where bacterial growth and  
6 migration are rife.

7

8 Preferably, said glass is adapted by the use of glass  
9 modifiers to give a sustained release of silver over a  
10 set period. The means to maintain the substance in  
11 contact with the surface may be a carrier combined with  
12 the glass or could be separate from the glass. If used  
13 alone, the glass may be in the form of a powder, as  
14 granules, as fibres that can be woven into a dressing  
15 form, as a sinter which may be shaped in a particular  
16 way, or cast into the required shape eg a collar to  
17 surround the area of penetration of a catheter into the  
18 body.

19

20 When combined with a carrier the glass may be used as a  
21 filler in polymers for surface release eg in silicones,  
22 natural and synthetic rubbers and medical plastics and  
23 polymers.

24

25 Alternatively, the glass may be incorporated in the  
26 adhesive of adhesive film dressings, in lint, wool, tow  
27 and gauze dressings and as part of wound management  
28 products such as foam, hydrogels and hydrocolloids,  
29 films, gels and creams.

30

31 Combinations of these examples can also be used.

32

33 According to a fourth aspect of the present invention,  
34 a water-soluble glass comprises an alkali metal oxide  
35  $M_2O$ , an alkaline earth oxide  $MO$ , phosphorus pentoxide

1  $P_2O_5$  and silver oxide ( $Ag_2O$ ).

2

3 Most preferably, said glass contains not more than 40  
4 mole %  $M_2O$  or  $MO$ , not less than 10 mole %  $M_2O$  or  $MO$ ,  
5 and not more than 50 mole % nor less than 38 mole %  
6 phosphorus pentoxide, with the inclusion of 0.05 to 5.0  
7 mole % silver oxide.

8

9 Said alkali metal oxide may be sodium oxide ( $Na_2O$ ),  
10 potassium ( $K_2O$ ) or a mixture thereof; and said alkaline  
11 earth oxide may be calcium oxide ( $CaO$ ), magnesium oxide  
12 ( $MgO$ ), zinc oxide ( $ZnO$ ) or a mixture thereof.

13

14 The glass may also contain less than 5 mole % silicon  
15 dioxide ( $SiO_2$ ), boric oxide ( $B_2O_3$ ), sulphate ion  
16 ( $SO_4^{2-}$ ), a halide ion, copper oxide ( $CuO$ ) or a mixture  
17 thereof.

18

19 Typically the soluble glasses used in this invention  
20 comprise phosphorus pentoxide ( $P_2O_5$ ) as the principal  
21 glass-former, together with any one or more  
22 glass-modifying non-toxic materials such as sodium  
23 oxide ( $Na_2O$ ), potassium oxide ( $K_2O$ ), magnesium oxide  
24 ( $MgO$ ), zinc oxide ( $ZnO$ ) and calcium oxide ( $CaO$ ). The  
25 rate at which the silver-release glass dissolves in  
26 fluids is determined by the glass composition,  
27 generally by the ratio of glass-modifier to  
28 glass-former and by the relative proportions of the  
29 glass-modifiers in the glass. By suitable adjustment  
30 of the glass composition, the dissolution rates in  
31 water at  $38^\circ C$  ranging from substantially zero to  
32  $25mg/cm^2/hour$  or more can be designed. However, the  
33 most desirable dissolution rate  $R$  of the glass is  
34 between  $0.01$  and  $2.0mg/cm^2/hour$ . The water-soluble  
35 glass is preferably a phosphate glass, and the silver

1 may advantageously be introduced during manufacture as  
2 silver orthophosphate ( $\text{Ag}_3\text{PO}_4$ ). The content of silver  
3 and other constituents in the glass can vary in  
4 accordance with conditions of use and desired rates of  
5 release, the content of silver generally being up to 5  
6 mole %. While we are following convention in  
7 describing the composition of the glass in terms of the  
8 mole % of oxides, of halides and of sulphate ions, this  
9 is not intended to imply that such chemical species are  
10 present in the glass nor that they are used for the  
11 batch for the preparation of the glass.

12  
13 The optimum rate of release of silver ions into an  
14 aqueous environment may be selected by circumstances  
15 and particularly by the specific function of the  
16 released silver. The invention provides a means of  
17 delivering silver ions to an aqueous medium at a rate  
18 which will maintain a concentration of silver ions in  
19 said aqueous medium of not less than 0.01 parts per  
20 million and not greater than 10 parts per million. In  
21 some cases, the required rate of release may be such  
22 that all of the silver added to the system is released  
23 in a short period of hours or days and in other  
24 applications it may be that the total silver be  
25 released slowly at a substantially uniform rate over a  
26 period extending to months or even years. In  
27 particular cases there may be additional requirements,  
28 for example it may be desirable that no residue remains  
29 after the source of the silver ions is exhausted or, in  
30 other cases, where the silver is made available it will  
31 be desirable that any materials, other than the silver  
32 itself, which are simultaneously released should be  
33 physiologically harmless. In yet other cases, it may  
34 be necessary to ensure that the pH of the resulting  
35 solution does not fall outside defined limits.

1  
2 The glass may be formed by a number of methods. It may  
3 simply be cast by conventional or centrifugal  
4 procedures, or it may be prepared via one or more  
5 stages of rod, fibre or tube drawing. Other  
6 preparation techniques include foamed glass or  
7 comminution of the glass followed by pressing and  
8 sintering into a solid body. It may be presented for  
9 example as a solid body, a powder or granules of  
10 preselected size, as flakes, or in the form of a number  
11 of hollow cylinders.

12  
13 A preparation of this invention may comprise a  
14 composite material containing one or more than one  
15 water-soluble glass composition. The antimicrobial  
16 properties of the preparation of the invention are due  
17 entirely to the bacteriostatic properties of silver  
18 ions.

19  
20 The antimicrobial properties of the preparation of the  
21 invention were demonstrated by placing a section of  
22 silver-containing water-soluble glass, cut from a 4mm  
23 rod, in culture medium. Over a period of 36 hours the  
24 growth of Pseudomonas aeruginosa was inhibited. A  
25 similar result was obtained when the culture medium was  
26 replaced with fluids recovered after use in Continuous  
27 Ambulatory Peritoneal Dialysis (CAPD). The inhibition  
28 of bacterial growth by slow release of silver has a  
29 wide range of application in those treatments where  
30 fluid enters or leaves the body by natural processes or  
31 by routes introduced by surgical intervention.

32

33 One such example exists in CAPD where patients with  
34 renal failure receive regular exchanges of dialysis  
35 fluid introduced into the peritoneal cavity. Delivery

1 is carried out under aseptic conditions from an  
2 individual bottle or plastic bag of sterile dialysis  
3 fluid via a resident catheter in the lower abdomen.  
4 Each time the circuit is broken there is a risk of  
5 infection both at the implant site and in the  
6 peritoneum which can lead to episodes of peritonitis  
7 and also to the required removal of the implanted  
8 catheter. The interposing of silver-release glass at  
9 the connector sites, through which liquid entering or  
10 leaving the peritoneal cavity flows, offers a barrier  
11 to bacterial invasion.

12  
13 Similarly, with parenteral infusions involving  
14 individual cannulae and catheters the incorporation of  
15 an antimicrobial barrier in accordance with this  
16 invention will reduce the risk to the patient.

17  
18 The antimicrobial action of silver is known. One of  
19 the most widely used silver-based pharmaceutical  
20 compositions is silver sulphadiazine which is commonly  
21 used, in the form of an ointment, for the treatment of  
22 burn wounds, (which are particularly subject to  
23 contamination by colonising organisms, especially  
24 bacteria and fungi), by topical application. In  
25 contact with the wound the silver sulphadiazine, both  
26 components possessing antibiotic properties. The  
27 compound also exhibits some degree of slow or sustained  
28 release of the silver and sulphadiazine because of its  
29 relatively low aqueous solubility which, of course,  
30 retards the dissociation necessary for release of the  
31 antibiotic action. Silver nitrate and silver  
32 allantoinate are also used.

33

34 Examples of preparations of water-soluble glasses  
35 containing silver (which are referred to below as

1 silver release inorganic polymers (SRP)) for use with  
2 the first three aspects of the invention are given in  
3 Table 1.

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1 TABLE 1

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3

4 GLASS CODE    Na<sub>2</sub>O mol%    CaO mol%    P<sub>2</sub>O<sub>5</sub> mol%    Ag<sub>2</sub>O as spec

5 -----

6

7 D060689-1        28            20            50            2 mole%

8

9 D060689-2        28            22            50            0 mole%

10

11 D281188-1        36            14            50            0 mole%

12

13 D041188-1        35            14            50            1 mole%

14

15 D011288-1        35            14            50            1 mole%

16

17 D221188-1        30            19            50            1 mole%

18

19 D141288-1        30            20            50            0 mole%

20

21 D100688-1        22            25            50            10 wt%

22

23 D070989-1        26            23.5          47            3.5 mole%

24

25 D141189-1        27.75        21.75        47            3.5 mole%

26

27 J290487-4        11.63        37.44        50.00        10 wt%

28

29 J010587-2        12.63        38.44        50.88        8 wt%

30

31

32

33

34 TABLE OF GLASS CODES GIVING COMPOSITION

35

1 SRP compositions D060689-1 (with silver) and D060689-2  
2 (without silver) were used to test effectiveness against  
3 organisms. Test discs of the SRP were placed on plain DST  
4 agar; one control and two test discs per plate. The  
5 plates were flooded with suspensions of test organisms,  
6 drained and dried. After incubation the widths of the  
7 zones of inhibition around the SRP discs were measured. In  
8 all cases the test samples gave significant zones of  
9 inhibition. In all cases, the controls (without silver)  
10 showed no zones of inhibition. The organisms tested were  
11 as follows: P vulgaris, P mirabilis, P rettgeri,  
12 Providencia spp., Ps aeruginosa, Staph. epidermidis, NCTC,  
13 E coli, Oxford Staph., C albicans, K aerogenes,  
14 Enterococcus, Ent cloacae. MRSA, Acinetobacter,  
15 S Marcescens. The full results of this test are shown in  
16 Table 2.

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1 TABLE 2

		24 hrs		48 hrs	
		Test	Control	Test	Control
		-----			
2					
3					
4					
5					
6	1. <u>Pro vulgaris</u>	6.25	0	6.25	0
7		6.25	0	6.25	0
8	2. <u>Pro mirabilis</u>	6.5	0	6.5	0
9		6.0	0	6.25	0
10	3. <u>Pro rettgeri</u>	5.0	0	4.25	0
11		4.75	0	4.25	0
12	4. <u>Ps.aeruginosa</u>	6.75	0	5.75	0
13		6.75	0	6.25	0
14	5. <u>Providencia spp</u>	5.75	0	3.75	0
15		5.5	0	3.75	0
16	6. <u>NCTC E coli</u>	6.75	0	6.75	0
17		6.75	0	6.75	0
18	7. <u>Oxford Staph</u>	5.75	0	5.25	0
19		5.75	0	5.25	0
20	8. <u>Staph epidermidis</u>	6.00	0	3.75	0
21		6.00	0	3.75	0
22	9. <u>C albicans</u>	10.00	0	0	0
23		9.00	0	0	0
24	10. <u>K aerogenes</u>	4.5	0	4.0	0
25		4.5	0	4.0	0
26	11. <u>Enterococcus</u>	1.5	0	1.5	0
27		1.75	0	1.75	0
28	12. <u>Ent Cloacae</u>	3.5	0	3.25	0
29		3.25	0	2.75	0
30	13. <u>MRSA</u>	5.25	0	5.75	0
31		5.0	0	5.75	0
32	14. <u>Acinetobacter</u>	5.5	0	5.75	0
33		5.25	0	5.75	0
34	15. <u>S marcescens</u>	6.0	0	5.5	0
35		5.5	0	5.5	0

1 SRP compositions D281188-1 (without silver), D041188-1  
2 (with silver) and D011288-1 (with silver) were subjected to  
3 gamma radiation and showed no significant change in the  
4 performance of the SRP. Samples of the SRP were tested  
5 after 0,1,2 and 3 exposures to 25 KGy of gamma irradiation.

6  
7 SRP composition D100688-1 (with silver) was used to test  
8 for skin reactions. Volunteers wore SRP impregnated  
9 patches for up to 10 days. No discomfort or irritation was  
10 reported. The SRP used in this test was composed of  
11 material to demonstrate the worst possible case.

12  
13 Incorporation of SRP composition D141189-1 (with silver)  
14 into silicone rubber sheeting has been demonstrated as a  
15 viable vehicle for the delivery of effective quantities of  
16 active silver ions. Silicone rubber sheets impregnated  
17 with SRP were cut into small discs and put onto agar which  
18 was then inoculated with various organisms. Again  
19 significant zones of inhibition were recorded and the  
20 results are shown in detail in Table 3. The SRP in the  
21 silicone samples has been formulated to release active  
22 silver ions over a 3-5 day period. Any period of release  
23 can be accommodated.

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1 TABLE 3

2

3 ORGANISMDISC

4

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A30 A15 B30 B15 B10 B5

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E coli

++ ++ ++ ++ ++ ++

7

Klebsiella sp

++ ++ ++ ++ ++ ++

8

Proteus sp

++ ++ ++ ++ ++ ++

9

Ps aeruginosa

++ ++ ++ ++ ++ ++

10

Staph aureus

+ + + + + -

11

Coag neg staph

+ + ++ + + -

12

MRSA

+ + ++ + + -

13

14

15 Table Zones of inhibition achieved by different silicon  
 16 discs against a range of organisms ( ++ = complete  
 17 inhibition of growth, + = partial inhibition of growth, - =  
 18 inhibition of growth).

19

20 Studies have also been carried out using SRP composition  
 21 D141189-1 (with silver) to assess systemic levels of silver  
 22 (from blood, urine, faeces surrounding tissue and vital  
 23 organs) in mice with silver releasing implants. No  
 24 readable level of silver was achieved except in the local  
 25 tissues, and possibly in blood and urine. Work with burns  
 26 patients treated with silver sulphadiazine has shown that  
 27 silver tends to remain local to its implant site showing  
 28 little ability to migrate through the tissues. Sheets of  
 29 silicone rubber containing 10%SRP were cut into discs  
 30 approximately 10 mm in diameter and 2mm thick. These were  
 31 implanted subcutaneously into three groups of three mice.  
 32 A fourth group contained three mice for control purposes  
 33 into which silicone samples without SRP were implanted.  
 34 Group 1 mice and one control were sacrificed on day 2,  
 35 group 2 and one control on day 5 and group 3 plus one

1 control on day 10. The samples from each group were  
2 prepared against standard solutions for analysis of silver  
3 levels by atomic absorption spectrophotometry. The  
4 implants showed only a mild local tissue reaction with  
5 silver present and no silver was detectable in the samples  
6 of vital organs.

7  
8 The ability of these SRP's, when incorporated in a dressing  
9 or dispersed in a carrier, to sustain the release of active  
10 levels of silver over a period of days or even weeks, if  
11 required, offers a simple and adaptable form of treatment  
12 which may be 'tailor-made' to requirements. Thus burn  
13 sepsis, surgical and traumatic wounds and ulcers and  
14 pressure sores may be effectively treated.  
15 Examples of the use of such SRP's are given below:

- 16  
17 a) If the SRP powder is mixed with a filler it may be  
18 pressed into the desired shape and then heated to fuse  
19 as a sinter in its final form.  
20  
21 b) Sheet material may be formed by mixing a  
22 polysaccharide such as alginate with SRP granules and  
23 subjecting the mix to a paper-making process so  
24 producing a board. Paper can be incorporated to give  
25 mechanical strength. In this way a dressing or a  
26 collar can be produced.  
27  
28 c) The SRP may be incorporated into silicon rubber and  
29 the rubber then applied to the treatment area, for  
30 example as a pad or collar. Catheter bodies, surface  
31 linings of cannulae, drainage tubes and the like, or  
32 superficial silicon coating of various instruments and  
33 appliances may be protected by rubber containing SRP.

34  
35 In such uses, the SRP-impregnated rubber may form the

1 entire wall thickness of the catheter or other tubing, or  
2 may be used in the form of a sleeve or coating on the outer  
3 face of a conventional catheter or tube whose wall is made  
4 of PVC or other material.

5  
6 A further important use of the present invention is in  
7 preventing bacteria spread and growth around punctures in  
8 the skin or around the entrance of body passages, for  
9 example the urethra. The areas around catheters which are  
10 in place for prolonged periods of time, or around stoma  
11 sites, are prone to bacterial residence and multiplication,  
12 and thus infection can arise. A collar of material used in  
13 the present invention can be applied around the catheter or  
14 stoma site in order to prevent proliferation of bacteria.

15  
16 The urethra, and hence the bladder, can also become  
17 infected by migration of bacteria in the perineal region,  
18 especially as the environment in that area is conducive to  
19 bacterial growth. To combat this, a pad, towel or tampon  
20 carrying SRP may be applied to the region; and the silver  
21 ions gradually released act as a bacteriostat or  
22 bactericide controlling the incidence and spread of  
23 bacteria over a prolonged period.

24  
25 The advantages derivable from the present Application  
26 include the following:

- 27  
28 (1) sustained and controlled release of silver ions to  
29 limit bacterial incidence and spread;  
30  
31 (2) small quantities of silver can be used to avoid  
32 electrolyte imbalance and minimise the risk of  
33 leukopenia, and also to reduce cost;  
34  
35 (3) the glass is biodegradable and so disappears from the

1 body without adverse effect;

2

3 (4) the glass is compatible with existing dressings and  
4 other topical applications;

5

6 (5) the exclusion of micro-organisms from the skin and  
7 wounds prevents their proliferation and limits their  
8 transfer from the site to ambient environment;

9

10 (6) the material used in the invention provides an  
11 environment conducive to healing; and

12

13 (7) trace elements such as zinc and magnesium can be  
14 included for additional beneficial effect.

15

16 Embodiments of the fourth aspect of the present invention  
17 will now be described by way of example with reference to  
18 the accompanying drawings, in which:

19

20 Fig. 1 is a side view of apparatus for use with the  
21 present invention;

22 Fig. 2(a) and (b) are side views of different forms of  
23 the apparatus in use;

24 Fig. 3 is a side sectional view of an alternative  
25 connection member of this apparatus;

26 Fig. 4 is a graph of the basic glass composition of  
27 the present invention in an  $\text{MO}$ ,  $\text{M}_2\text{O}$  and  $\text{P}_2\text{O}_5$  system;  
28 and,

29 Fig. 5 is a graph showing the pH of solution products  
30 as a function of  $\text{P}_2\text{O}_5$  content.

31

32 Referring to Fig. 1, the apparatus comprises an indwelling  
33 urinary catheter 2 having inflatable balloon portions 4, 6  
34 for maintaining the catheter in position in the urethra  
35 with the free end 8 in the bladder to collect urine through

1 apertures 10, 12. At the outer end the catheter 2  
2 terminates in a first portion 14 of a connector 16 whose  
3 second portion 18 leads to tubing 20 which enters a urine  
4 collection bottle 22. The bottle 22 has at its lower end  
5 remote from the tubing 20 a drain plug 24. The connection  
6 between the first and second portions 14, 18 of the  
7 connector represents a site of potential contamination by  
8 bacteria which can be introduced on releasing the connector  
9 16, for example to change the bottle 22 and tubing 20.

10

11 The urine itself is contaminated and the bacteria can  
12 reproduce in the bottle 22 as the urine collects in it..  
13 Thus when a nurse empties the bottle 22 through the drain  
14 plug 24 there is a risk of bacteria being transferred to  
15 the nurse. Further, bacteria in the bottle may find their  
16 way along the tubing 20, connector 16 and catheter 2 into  
17 the patient's bladder, causing infection.

18.

19

20 In order to prevent such infection by bacterial  
21 reproduction and transfer, the first portion 18 of the  
22 connector 16 has a peripheral recess 26 defined by spaced  
23 shoulders 28, 30, and a sleeve or lining 32 of  
24 water-soluble glass impregnated with silver is retained in  
25 the recess 26 to form part of the flow passageway for urine  
26 through the connector. Further, the bottle 22 contains a  
27 braided pouch 34 within which are held granules of the  
28 impregnated water-soluble glass, the pouch being tubular  
29 and closed at each end. The material of the pouch 34 is  
30 such that it contains interstices which allow urine to pass  
31 through but which are small enough to prevent the granules  
32 of the glass escaping.

33

34 In use the glass sleeve 32 and the glass in the pouch 34  
35 act as a bacteriostat preventing an increase in the number

1 of bacteria in the urine itself and of bacteria introduced  
2 in the event of the connector 16 being opened, for example  
3 to change the bottle 22. This occurs by virtue of the  
4 gradual dissolution of the glass, releasing the silver with  
5 its bacteriostatic properties over a prolonged period. The  
6 composition of the glass determines the rate of silver  
7 release.

8  
9 Fig. 2(a) illustrates the use of a connector 16, which is  
10 of similar construction to that shown in Fig. 1, in  
11 peritoneal dialysis in which fluid passes from a reservoir  
12 38 into the peritoneum of the patient. In this case the  
13 fluid itself is sterile so the reservoir 38 need not  
14 contain a pouch 34 as in Fig. 1, but the sleeve 32 is  
15 required in the connector 16 to deal with bacteria which  
16 may be introduced when the connector is opened in order to  
17 replace the reservoir 38 when empty. Fig. 2(b) illustrates  
18 the apparatus in post-surgical drainage, in which suction  
19 is applied through a line 40 to the patient to draw fluid  
20 from the operation site into a collection bottle 42.  
21 Again, the connector 16 is of similar construction to that  
22 of Fig. 1 and includes the silver-impregnated sleeve 32.

23  
24 Referring now to Fig. 3, the connector 16 has first and  
25 second portions 14, 18 having an ingot 44 of  
26 silver-containing water-soluble glass between them. The  
27 ingot 44 is in the form of a solid sleeve 46 having an  
28 annular flange 48 at one end to bear against an end face of  
29 the second portion 18. The first and second portions 14,  
30 18 each have a fitting 49, 50 for receiving an end portion  
31 of rubber tubing. The sleeve 46 fits within the first  
32 portion 14 so as to contact fluid passing through the  
33 connector 16.

34  
35 In the connector of Fig. 3, the ingot 44 is made by mixing



1 together 35 mole % of  $\text{NaH}_2\text{PO}_4$ , 15 mole % of  $\text{CaHPO}_4$  and 50  
2 mole % of  $\text{P}_2\text{O}_5$ , heating the mixture at  $1050^\circ\text{C}$  for 20  
3 minutes, and cooling and grinding the glass thus obtained  
4 until it forms a powder. This powder is then weighed and  
5 up to 10% by weight of silver orthophosphate ( $\text{Ag}_3\text{PO}_4$ ) is  
6 added and mixed in. The mixture is then heated to  $1050^\circ\text{C}$   
7 to produce a homogeneous impregnated water-soluble glass,  
8 cast into shape and annealed.

9  
10 The granulated form of the glass provided in the pouch 34  
11 of Fig. 1 can also be made in this way, with a final  
12 granulation stage instead of casting.

13  
14 Alternatively the silver orthophosphate can be included in  
15 the original mix to allow a single heating stage.

16  
17 It has been found that if the silver-impregnated  
18 water-soluble glass used in these embodiments of the  
19 invention is heated directly at its surface after its  
20 manufacture, in a manner that creates a rapid temperature  
21 gradient through the material, elemental silver forms at  
22 the surface in a fine layer which in use provides an  
23 initial increased rate of dissolution of the silver into  
24 the fluid until the surface layer has all dissolved, after  
25 which the glass dissolves as normal with a slower rate of  
26 release of silver. In producing this effect it is  
27 important that the heating is not sustained after the  
28 formation of the silver surface layer as the glass  
29 otherwise may devitrify and the release rate of the silver  
30 becomes unpredictable.

31  
32 The glass is dissolved by the breakup of the 3-D  
33 phosphorus-oxygen skeleton by the attacking  $\text{H}^+$  and  $\text{OH}^-$  ions  
34 and molecular  $\text{H}_2\text{O}$  causing the release of phosphorus-oxygen  
35 fragments and associated cations.

1 GLASS + WATER PHOSPHATE IONS + INCOMPLETE IONS  
 2  
 3  $(H^+, OH^-, H_2O) (P_n O_{3n+1})^{(n+2)-}$  eg.  $(HPO_4)^{2-}$   
 4

5 The solution rate of the glass is approximately equal to  
 6 the sum of the reactions of  $H^+$ ,  $OH^-$  and  $H_2O$  with glass.  
 7 The attack by  $H^+$  is the fastest, hence the solution rate,  
 8  $R$ , is a monotonic function of the hydrogen ion  
 9 concentration, (except in very alkaline solutions).

10  
 11 The pH of solution due to the dissolution of products is  
 12 dependent on the composition of the glass in the ratio  
 13  $(M_2O+MO)/P_2O_5$  and in the volume and flow-rate of the  
 14 aqueous solvent.

15  
 16 Fig. 4 shows a graph indicating the limits of the glass  
 17 composition in the  $MO$ ,  $M_2O$  and  $P_2O_5$  system. The shaded  
 18 area describes the most desirable composition, ie. 38-50  
 19 mole % phosphorus pentoxide and 10-40 mole %  $M_2O$  (eg.  
 20 sodium oxide) and  $MO$  (eg. calcium oxide) assuming the  
 21 inclusion of 0.05-5.0 mole % silver oxide. Adverse effects  
 22 of pH on solution rate can be controlled by alteration to  
 23 the basic glass composition.

24  
 25 Fig. 5 shows this in the form of a graph showing the pH of  
 26 the solution products of 2 g/l of glasses of varying  
 27 composition, which have completely dissolved (ie. a  
 28 concentration of 20mMol approximately).

29  
 30 It is understood that the solution rate,  $R$ , of the glass is  
 31 also, to some extent, dependent on the pH of the aqueous  
 32 solvent. We chose to specify the solution rate,  $R$ , as mg  
 33 of glass per  $cm^2$  per hour by water of pH 7.0 at 38°C.  
 34 While the solution rate does not change significantly as  
 35 the pH is changed from 9-4, at values of  $pH < 4.0$  the

1 solution rate increases rapidly as the solvent becomes more  
2 acid. It will be clear that if the glass is to be used in  
3 aqueous solutions with a pH outside the range 4-8 the  
4 composition of the glass should be selected to give the  
5 required solution rate in an aqueous solvent of this  
6 particular pH.

7  
8 The temperature dependence of solution rate is the  
9 temperature dependence of the chemical reaction and is of  
10 the general form:  $R=R_0e^{-A/KT}$  where A is the activation  
11 energy of the solution reaction and is such that the  
12 solution rate, R, doubles for each 10°C rise in  
13 temperature.

14  
15 Experiments using the invention will now be described by  
16 way of example.

17  
18 The silver-impregnated water-soluble glass was produced in  
19 two forms which would enable its incorporation into the  
20 urinary catheter collection system of Fig. 1 but using the  
21 connector shown in Fig. 3:

22  
23 1. A silver-impregnated glass ingot inside a plastic  
24 connector which would be situated between the distal end of  
25 the catheter and the proximal end of the urine collection  
26 bag tubing. The reason for siting the silver glass here is  
27 that many episodes of urinary tract infection in  
28 catheterised patients are thought to result from  
29 contamination of the catheter/bag junction when the  
30 collection bag is disconnected and reconnected.

31  
32 2. A porous plastic pouch containing small granules of  
33 silver-impregnated glass which would be situated inside the  
34 collection bag releasing silver ions into the collected  
35 urine. This would reduce the numbers of bacteria present

1 in the collection bag which is thought to be a potential  
2 source of cross-infection in wards where there are several  
3 catheterised patients.

4  
5 Experiment 1

6  
7 Brain heart infusion broth containing small pellets of  
8 silver-impregnated glass were inoculated with small numbers  
9 of different test organisms and the broths incubated at  
10 37°C overnight. Test organisms used were

11  
12 Escherichia coli

13 Pseudomonas aeruginosa

14 Proteus mirabilis

15 Klebsiella sp

16 Staphylococcus aureus

17 Staphylococcus epidermidis

18  
19 The broths were subcultured after 48 hours to assess  
20 whether bacterial growth had been inhibited or not.  
21 Control cultures were also set up which did not contain  
22 silver-impregnated glass pellets.

23  
24 Experiment 2

25  
26 Pooled samples of urine containing varying numbers of  
27 bacteria ranging from  $1 \times 10^5$  to  $1 \times 10^7$  organisms per ml  
28 of urine were run through the silver-impregnated glass  
29 ingot containing connector at the rate of 1 ml per minute  
30 (the approximate rate at which urine flows through a  
31 urinary catheter) for 2 hours. The number of organisms  
32 present in the urine before and after flowing through the  
33 connector and after incubation of the collected urine at  
34 room temperature for 24 hours were estimated. These were  
35 compared to the numbers of organisms present in similar

1 samples of the pooled urine which had not been passed  
2 through the connector.

3

4 Experiment 3

5

6 Filtered (sterile) urine was run through the  
7 silver-impregnated glass connector at the rate of 1 ml per  
8 minute for 2 hours as before. The connector was then  
9 artificially contaminated with  $1 \times 10^6$  organisms of E.coli  
10 and sterile urine run through the connector for a further 1  
11 hour. This was to simulate contamination of the connector  
12 for a further 1 hour. This was to simulate contamination  
13 of the connector during changing of the collection bag.  
14 The number of organisms present in the collected urine was  
15 estimated immediately after collection (Time 0) and after  
16 24, 48, 72 and 96 hours' incubation at room temperature.

17

18 This experiment was also carried out using nutrient broth  
19 instead of sterile urine (when urine was unavailable).

20

21 Experiment 4

22

23 Sterile urine was allowed to flow through the  
24 silver-impregnated glass connector at the rate of 1 ml per  
25 minute for 24 hours. Several samples were taken during  
26 this time for silver estimation in order to gain a picture  
27 of the rate of silver release into the collected urine.

28

29 Experiment 5

30

31 Filtered (sterile) urine was collected in a container  
32 containing silver-impregnated water-soluble glass granules  
33 in a braided plastic pouch. This urine was then  
34 artificially contaminated with a known number of organisms  
35 of E. coli and the collected urine incubated at room

1 temperature for 4 days, the numbers of organisms present in  
2 the urine being estimated daily.

3

#### 4 Results

5

6 Preliminary experiments which assessed the ability of  
7 silver-impregnated glass to inhibit the growth of different  
8 types of bacteria showed that the glass pellets inhibited  
9 the growth of all types of bacteria except the Proteus  
10 mirabilis.

11

12 In Experiment 2, passing the urine through the connector  
13 did not immediately reduce the numbers of organisms present  
14 in the urine, but after 24 hours' incubation there was  
15 approximately a ten-fold reduction in the numbers of  
16 organisms in the urine which had been passed through the  
17 connector when compared with the control urine.

18

19 When sterile urine or nutrient broth was used and the  
20 connector artificially contaminated with E. coli, the  
21 numbers of organisms in the control urine had significantly  
22 multiplied after 24 hours' incubation, but the test urine  
23 which had been passed through the connector showed very  
24 small numbers of organisms present after 24 and 48 hours  
25 and regrowth of the E. coli did not occur until after 72 or  
26 96 hours' incubation.

27

28 The preliminary results of the experiments assessing the  
29 use of the plastic pouch containing silver-impregnated  
30 glass granules to inhibit organism growth gave positive  
31 results.

32

33 Both the glass-containing connector and the plastic pouch  
34 containing glass granules released enough silver to inhibit  
35 the growth of bacteria and can be incorporated into urinary

1 collection systems in order to reduce the risk of urinary  
2 tract infection in catheterised patients.

3

4 In the above Experiments the ingot contained in the  
5 connector comprised 35 mole %  $\text{NaH}_2\text{PO}_4$ , 15 mole %  $\text{CaHPO}_4$  and  
6 50 mole %  $\text{P}_2\text{O}_5$ , and 10% by weight of silver. This resulted  
7 in a rate of release of silver of 1mg per  $\text{cm}^2$  per hour.

8

9 The granules in the plastic pouch comprised 25 mole %  
10  $\text{NaH}_2\text{PO}_4$ , 25 mole %  $\text{CaHPO}_4$  and 50 mole %  $\text{P}_2\text{O}_5$ , with 5% by  
11 weight of silver. The silver release rate was 0.6mg per  
12  $\text{cm}^2$  per hour.

13

14 In general, an increase in the amount of sodium present in  
15 the glass increases the rate of dissolution and therefore  
16 of silver release when the  $\text{P}_2\text{O}_5$  content remains constant.

17

18 Modifications and improvements may be incorporated without  
19 departing from the scope of the invention.

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

1    CLAIMS

2

3

4    1.    A medicinal substance for topical application  
5           comprising a water-soluble glass containing elemental  
6           silver or a silver compound and means to maintain the  
7           substance in contact with a surface of a body.

8

9    2.    A medicinal substance according to Claim 1, wherein  
10          the water-soluble glass contains silver oxide.

11

12    3.    A medicinal substance according to Claim 2, wherein  
13          there is less than substantially 5 mole% of silver  
14          oxide.

15

16    4.    A medicinal substance according to any of Claims 1 to  
17          3, wherein the water-soluble glass comprises  
18          phosphorus pentoxide.

19

20    5.    A medicinal substance according to any of Claims 1 to  
21          3, wherein the substance is in the form of a powder.

22

23    6.    A medicinal substance according to any of Claims 1 to  
24          3, wherein the substance is in the form of fibres  
25          woven into a dressing form.

26

27    7.    A medicinal substance according to any of Claims 1 to  
28          3, wherein the substance is in the form of a sinter.

29

30    8.    A medicinal substance according to any of Claims 1 to  
31          3, further comprising a polymer in which the glass is  
32          used as a filler for surface release.

33

34    9.    A method of retarding bacterial growth at the surface  
35          of a body comprising applying a water-soluble glass



1       impregnated with elemental silver or a silver compound  
2       to the surface and maintaining the glass in contact  
3       with the surface.  
4

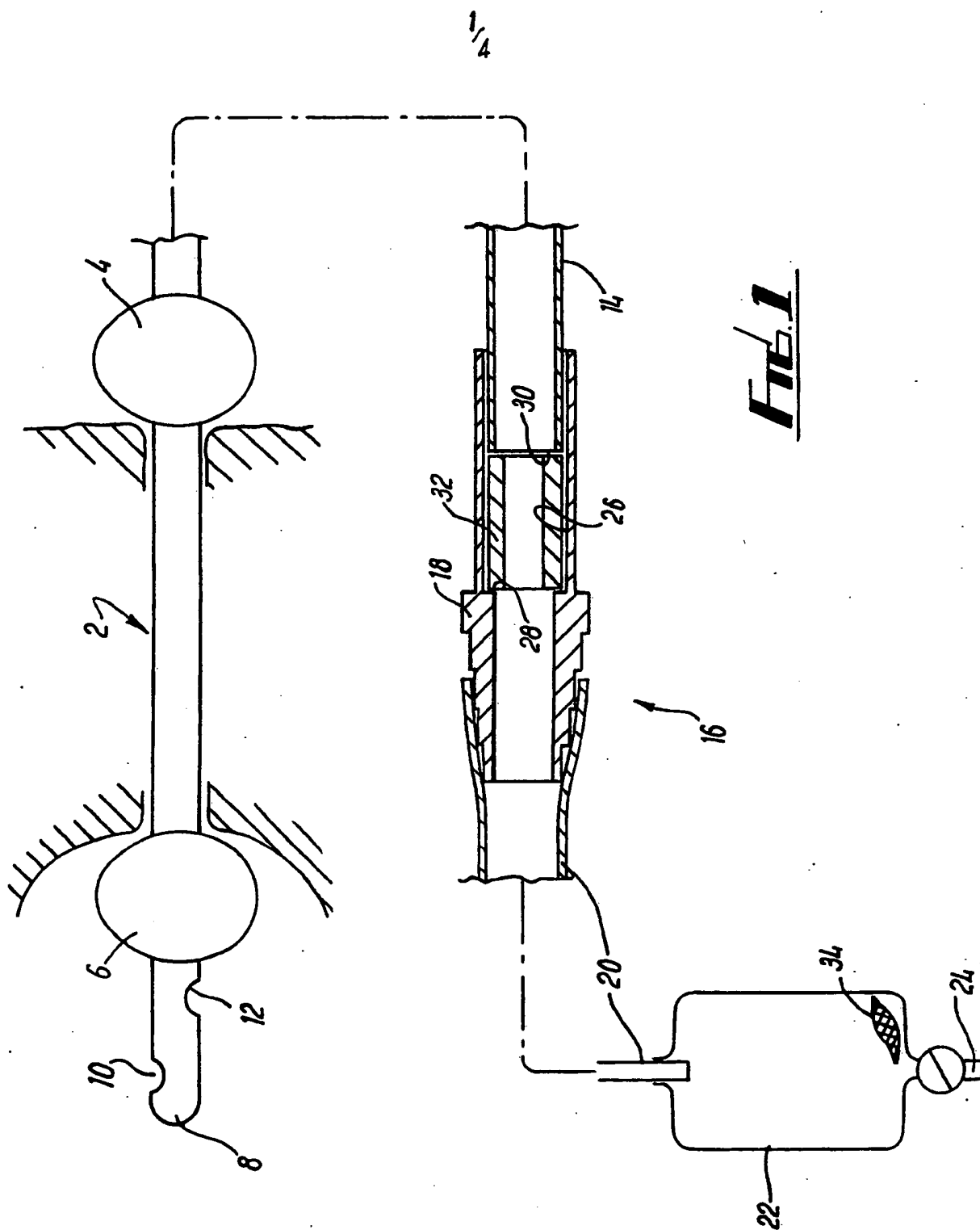
5       10. The use of water-soluble glass containing elemental  
6       silver or a compound of silver in the preparation of a  
7       medicament for the treatment of wounds and other  
8       topical infection sites.  
9

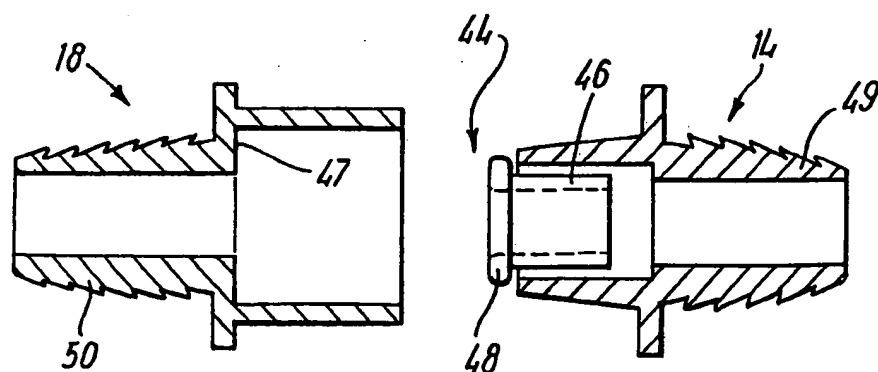
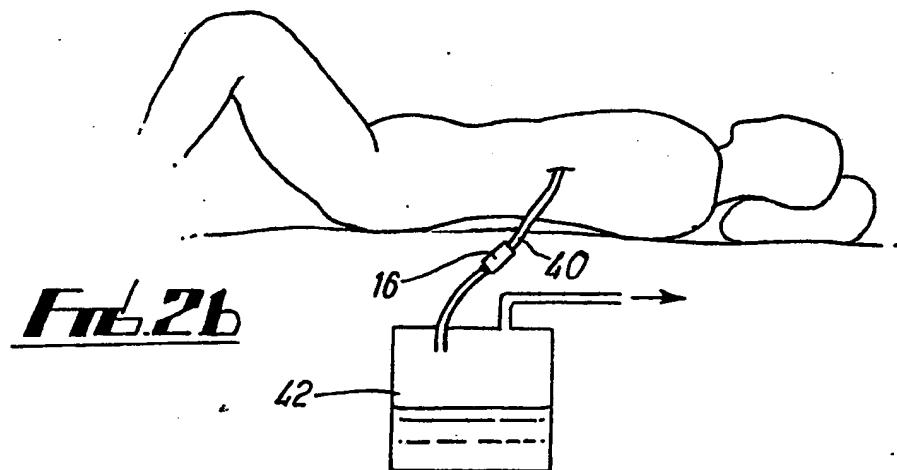
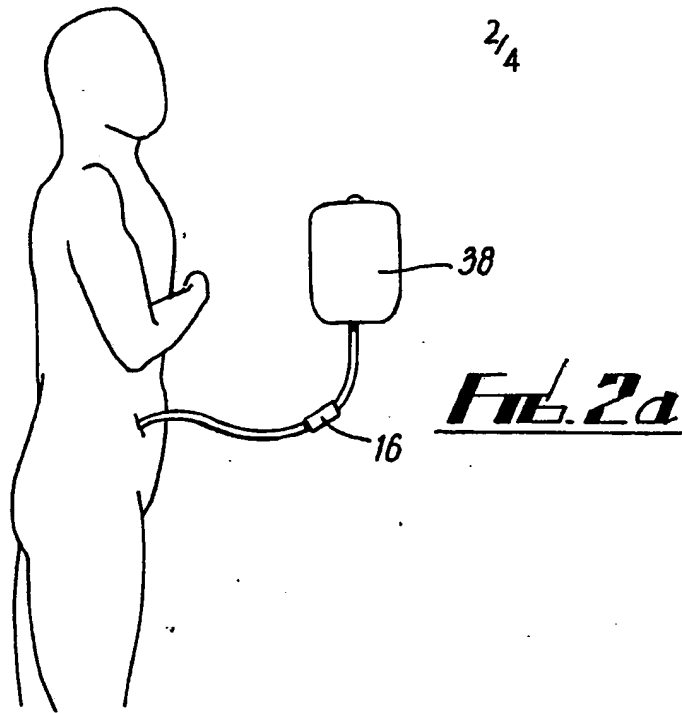
10      11. A water-soluble glass comprising an alkali metal oxide  
11       $M_2O$ , an alkaline earth oxide  $MO$ , phosphorus pentoxide  
12       $P_2O_5$  and silver oxide ( $Ag_2O$ ).  
13

14      12. A water-soluble glass according to Claim 11, wherein  
15      the glass contains substantially between 10 to 40 mole  
16      %  $M_2O$  or  $MO$ .  
17

18      13. A water-soluble glass according to Claim 11, wherein  
19      the glass contains substantially between 38 to 50 mole  
20      % phosphorus pentoxide.  
21

22      14. A water-soluble glass according to Claim 11, wherein  
23      the glass contains substantially between 0.05 to 5.0  
24      mole % silver oxide.  
25  
26  
27  
28  
29  
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31  
32  
33  
34  
35





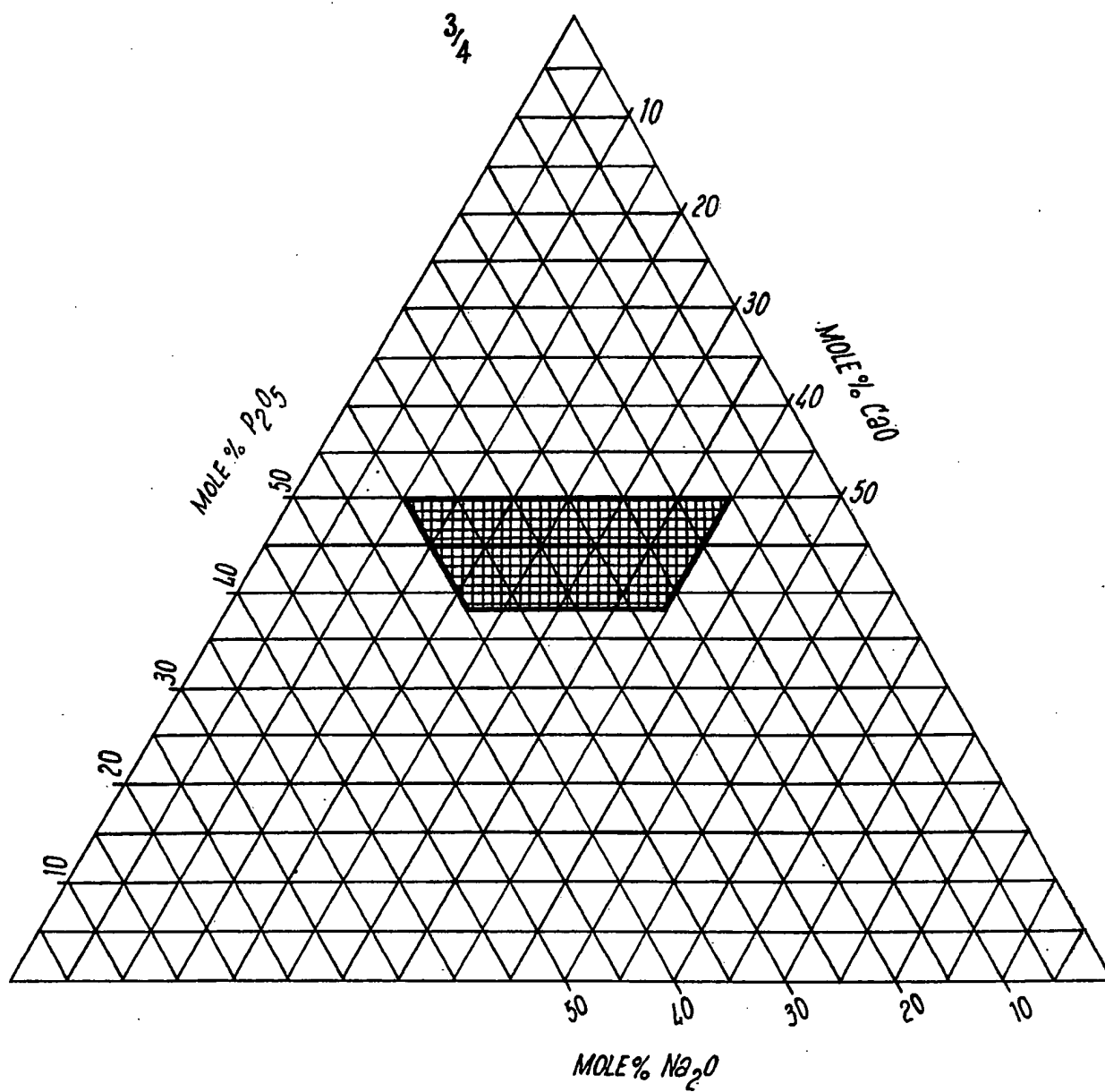
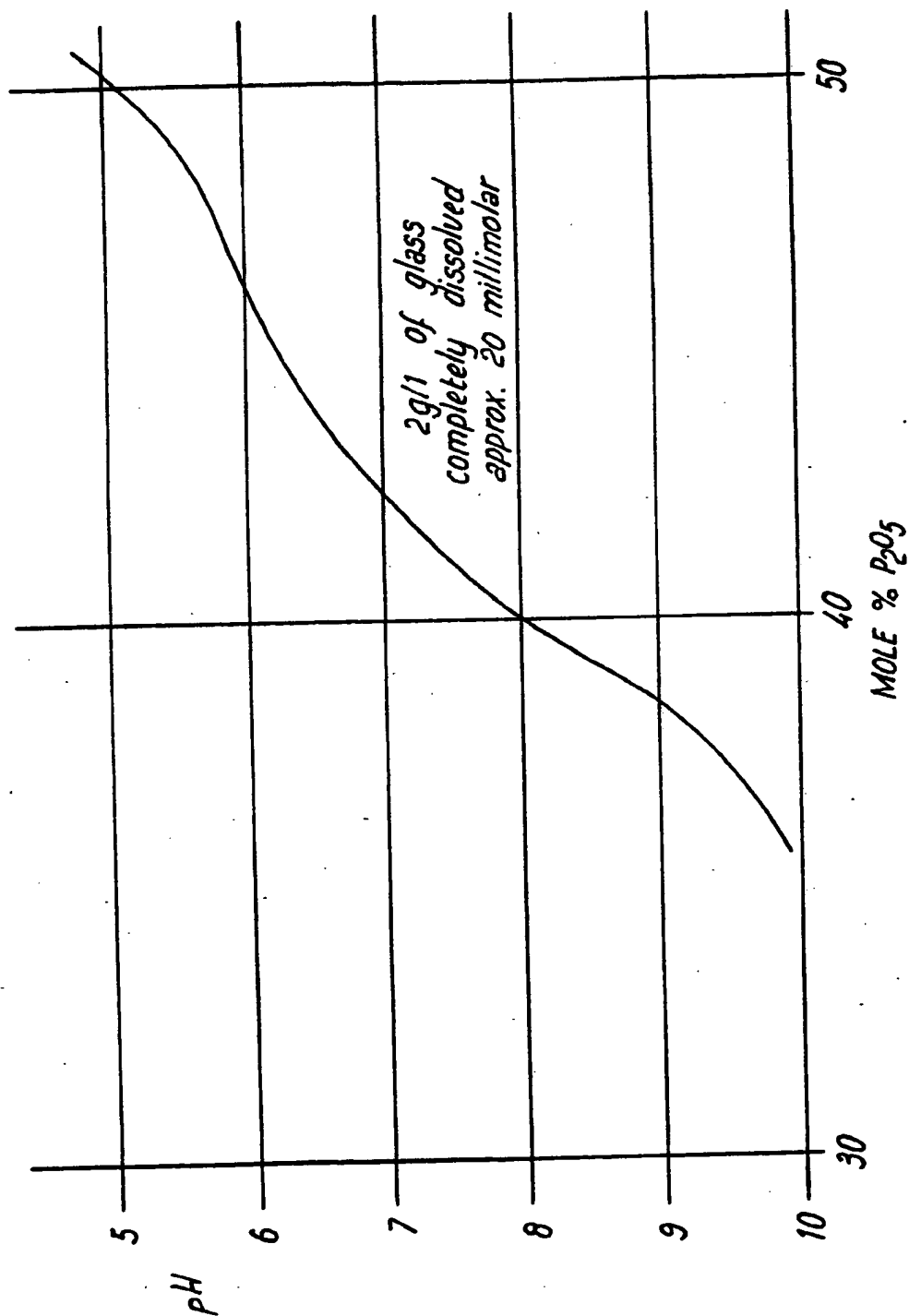


FIG. 4


4/4



**Fig. 5**

# INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 90/00125

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC <sup>5</sup> A 01 N 59/16, A 01 N 25/34, A 01 N 25/12, A 61 L 29/00, IPC: A 61 L 2/00, A 61 K 33/38		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
IPC <sup>5</sup>	A 01 N, A 61 K, A 61 L	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	DE, C, 3726617 (FRIEDRICHSFELD GmbH KERAMIK- UND KUNSTSTOFFWERKE) 7 July 1988 see column 3, lines 25-29; claims 1-2,4,9,11,13-16	1,6,8-10
	--	
X	WO, A, 85/01210 (THE UNIVERSITY OF STRATHCLYDE) 28 March 1985 see page 2, lines 16-25; page 4, lines 18-21; page 6, lines 12-23; claims 1,3-4	1,4-5,7,9-10
Y		2-3
	--	
X	US, A, 2510510 (E.E. MENDENHALL) 6 June 1950 see column 3, line 68 - column 4, line 23; column 15, lines 1-8;	11-14
<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p><sup>*</sup> Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"A" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
14th May 1990	13.06.90	
International Searching Authority	Signature of Authorised Officer	
EUROPEAN PATENT OFFICE	 MISS T. TAZELAAR	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	claims 1-3  --	2-3
A	EP, A, 0080330 (STANDARD TELEPHONES AND CABLES PLC) 1 June 1983 see page 4, lines 4-26; page 6, lines 24-32; claims 1,6-7,9,10  --	1-14
A	GB, A, 1565906 (STANDARD TELEPHONES AND CABLES LTD) 23 April 1980 see page 2, lines 13-24; claims 1-4 (cited in the application)  -----	1-14

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9000125

SA 34143

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 12/06/90  
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